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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/874,141	ANDERSON ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5,16-28,30 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5,16-28,30 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 3/14/06 has been entered.

Applicant's amendment, filed 3/14/06, has been entered.

Claims 1, 4, 6-15, 29, 31 and 32 have been canceled previously.

Claims 2, 18, 30, 32, 33 and 34 have been amended.

Claims 2, 3, 5, 16-28, 30, and 33-38 are pending.

Applicant's election with traverse of multiple sclerosis (Group II-C) as the disease species has been acknowledged.

Claims 2, 3, 5, 16-28, 30 and 33-38 as they read on treating multiple sclerosis with anti-gp39 antibodies are under consideration as the elected invention.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

This Action will be in response to applicant's amendment, filed 7/8/05, which appears to reiterate applicant's previously amendment, filed 4/12/05.

The rejections of record can be found in the previous Office Action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The amendment filed 3/14/06 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

The added material which is not supported by the original disclosure is as follows:

Applicant's amendment to correct errors in the description of the P and E modifications and to update the status of the Attorney Docket No. is acknowledged.

Applicant's reliance on certain facts (e.g. Angal et al., Mol. Immunol. 30: 105-108, 1993; Duncan et al., Nature 332: 563-564, 1988) and what was known to the skilled artisan at the time the invention well is acknowledged.

However, given applicant's amendment to correct errors in the description of sequences after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material are the biological materials specifically identified in the application as filed and to explain the modifications.

5. Claims 2, 3, 5, 16-28, 30 and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:

the step of "assaying in vitro to identify anti-human gp39 antibodies that are non-agonistic of an activation response by purified $CD4^+$ T cells".

Applicant's amendment, filed 3/14/06, directs support to pages 35-36 of the instant specification) for the written support for the step of "assaying in vitro to identify anti-human gp39 antibodies that are non-agonistic of an activation response by purified $CD4^+$ T cells".

However, pages 35-37 of the instant specification do not provide sufficient written description for the "in vitro assay step" "with purified $CD4^+$ T cells".

Applicant's reliance on generic disclosure of identifying "antibodies that do not agonize T cell activation, but still prevent T cell / B cell interactions based upon T cell activation" and the use of purified $CD4^+$ T cell in stimulating sub-optimal primed T cells under certain conditions does not provide sufficient direction and guidance to the "limitations", as currently claimed.

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The specification as filed does not provide a written description or set forth the metes and bounds of this phrase. The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.

See MPEP 714.02 and 2163.06

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 2, 3, 5, 16-28, 30 and 33-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Black et al. (U.S. Patent No. 6,001,358) in view of the art known methods to screen for inhibitors of cytokines and proliferation in view of Schrader et al. (U.S. Patent No. 5,627,052), Burkly et al. (US2002/0028202 A1) and Wilson et al. (U.S. Patent No. 6,372,208 B1) essentially for the reasons of record
AND in further view of newly added Van den Eertwegh et al. (J. Exp. Med. 178: 1555-1565, 1993) and Roy et al. (J. Immunol. 151: 2497-2510, 1993).

Applicant's arguments, filed 7/8/05, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Newly added Van den Eertwegh et al. (J. Exp. Med. 178: 1555-1565, 1993) and Roy et al. (J. Immunol. 151: 2497-2510, 1993) have been provided to make the record clear the CD40 ligand expressing cells involved in T – B cell interactions were associated and analyzed in the context of IL-2, IL-4 and interferon γ at the time the invention was made.

Van den Eertwegh et al. teach evaluating or analyzing cytokine production associated with IL-2, IL-4 and interferon γ in the context of CD40 ligand- / gp39-expressing T cells in the context of T – B cell interactions in vitro and in vivo and that CD40L gp39 T cell and cytokine producing cell are simultaneously upregulated after immunization (e.g. see Discussion, including the last paragraph on page 1563) (see entire document, including Summary).

Roy et al. teach the regulation of gp39 / CD40 ligand on normal and cloned human $CD4^+$ T cells and the importance of the expression of CD40 ligand on activated T cells in determining effector function (see entire document, including the Discussion). Here, the studies were conducted with purified CD4 T cells and analysis of IL-2, IL-4 and interferon γ (e.g., see Materials and Methods and Results).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Van den Eertwegh et al and Roy et al. to the teachings of Schrader et al., Burkly et al. and Wilson et al. as well as to those of Black et al. to screen and obtain antagonistic anti-gp39 antibodies with the ability to inhibit cytokines produced by activated T cells, including the inhibition of IL-2, IL-4 and γ-interferon, which were known to be products of the T cells targeted by antagonistic anti-gp39 antibodies, including purified $CD4^+$ T cells.

Van den Eertwegh et al and Roy et al. provided further evidence that the ordinary artisan understood the importance and role of CD40 ligand expressing T cells and cytokine production in the elaboration of immune response in the context of T-B cell interactions and subsequent effector functions. Note too, that human B cells were known antigen presenting cells at the time the invention was made.

Also, as noted previously, a person of ordinary skill in the art would have been motivated to produce this resultant ability of anti-gp39 antibodies to inhibit cytokine activity by activated T cells in order to test and select for those anti-gp39 antibodies that had the described properties of inhibiting gp39:CD40 interaction and the resultant ability of such antibodies to inhibit T cell mediated activation of immune response in the treatment of various conditions and disorders, including multiple sclerosis.

As indicated previously, once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the secondary references, including the newly added Van den Eertwegh et al and Roy et al. which clearly provide for the importance of CD40 ligand expressing T cells and subsequent effector functions in the context of IL-2, IL-4 and γ-interferon provide clear teachings of the known assays to test inhibitory antibodies, antibodies that inhibit T cell activation and proliferation, including antibodies that inhibit CD40 ligand : CD40 interactions.

Both Black et al. and Wilson et al. teach inhibitory anti-CD40 ligand (anti-gp39) antibodies and their effects on T cell mediated activation and functions.

Given the role of various cytokines such as IL-2, IL-4 and γ-interferon, which were known to be products of the T cells targeted by antagonistic anti-gp39 antibodies, play in immune responses, one of ordinary skill in the art would have been motivated to screen and test for the properties of antagonistic anti-CD40 ligand antibodies that inhibited T cell activation and proliferation in the selection of such inhibitory antibodies that can regulate the various manifestations of T cell activation and function.

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144

Applicant's arguments are not persuasive.

The following of record is reiterated for applicant's convenience.

Black et al. teach methods of treating disease condition wherein gp39 inhibition is therapeutically beneficial (columns 13-14 and 31-34), including multiple sclerosis with column 14, line 40 and column 32, line 67) with antibodies that bind gp39 (CD40 ligand), which block signals delivered via CD40 (See Examples 2, 3 columns 22-23; Examples 11-17 on columns 28-38 (see entire document).

In addition, Black et al. teach chimeric, humanized, and primatized antibodies, including the use of different heavy chain constant regions (IgG1, IgG3, IgG4), with conservative amino acid substitutions such as Kabat positions 229 and 236 as well as the 24-31 antibody specificity and its variable regions amino acid sequences encompassed by the claimed methods (see entire document, including Background of the Invention, including columns 6-7; Summary of the Invention; Detailed Description of the Invention, including columns 13-22; Claims). Further, it is noted that Black et al. teach that it was known that $gp39^+$ T cells produced IL-2, IL-4 and ϒ-interferon (see column 4, paragraph 1). In addition, Black et al. teach modes of administration and dosages of antagonistic anti-gp39 antibodies encompassed by the claimed methods (see columns 33-38).

Again, applicant asserts that Black et al. does not describe or suggest a method of obtaining anti-gp39 antibodies that includes steps of assaying for and identifying non-agonistic antibodies with the characteristics of human T cell activation.

While applicant has relied upon the teachings of Blair et al. (J. Exp. Med. 191: 651-660, 2000) and Blotta et al. (J. Immunol. 156: 3133-3140. 1996) to indicate the agonistic properties of anti-gp39 antibodies on T cells,

it was noted that these references appear to rely upon the cross-linking of anti-gp39 antibodies to achieve such agonistic properties.

While applicant has also relied upon the data in Table 5 of Black and the possible distinctions between anti-mouse gp39 antibodies versus anti-human gp39 antibodies to support the unobviousness of the prior art rejection,

it has been pointed out that both Black et al. and Wilson et al. teach inhibitory anti-CD40 ligand (anti-gp39) antibodies and their effects on T cell mediated activation and functions and that Wilson et al. makes no distinction between inhibitory anti-mouse gp39 antibodies versus anti-human gp39 antibodies.

Black et al. differs from the claimed methods by not disclosing the art known use of screening for inhibitors of cytokine activity such as IL-2, IL-4 and ϒ-interferon as well as cell proliferation per se in selecting antagonistic anti-gp39 antibodies.

Schrader et al. teach methods of producing antibodies of a desired function to a variety of antigens, including IL-2 and ϒ-interferon, including the section of antibodies that neutralizes a growth factor or detection of antibodies that neutralize IL-2 (e.g. see columns 8-9, overlapping paragraph) and exemplifies the detection of antibodies that neutralize IL-2 (see Example 1 on columns 21-22) (see entire document, including Summary of the Invention and Detailed Description of the Invention).

Burkly et al. teach known methods of assaying or screening the ability of antagonists such as antibodies to block a response to a particular cytokine (e.g. IL-2) (See GC Chain Blocking Agents and Production of GC Blocking Antibodies on pages 7-8 and Testing Compounds of the Invention for Biological Utility on page 13). Burkly et al. note that it will be recognized by one skilled in the art, that these screens can be arranged to discover antibodies whose activities are conspicuous in one or more of these assays (see paragraph 095 on page 8) and that one of skill in art may easily determined using well known methods whether a particular blocking agent displays biological activity (see Testing Compounds of the Invention for Biological Utility on page 13).

Wilson et al. teach that CD40 ligand – CD40 interactions are desirable given its broad activity in both T helper cell activation and function as well as the absence of redundancy in its signaling pathway (see entire document, particularly column 6, paragraphs 4-5). In addition, Example 8 describes analyzing the effect of CD40 ligand blockade with antibodies on T cell activation using both in vitro and in vivo assays, including T cell proliferation (see columns 20-22).

While applicant appears to focus on the vivo testing aspects of the teachings of Wilson et al., the combined references, including Wilson et al. of record and the newly added Van den Eertwegh et al and Roy et al. which clearly provide for the importance of CD40 ligand expressing T cells and subsequent effector functions in the context of IL-2, IL-4 and γ-interferon provide clear teachings of the known assays to test inhibitory antibodies, antibodies that inhibit T cell activation and proliferation, including antibodies that inhibit CD40 ligand : CD40 interactions.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of newly added Van den Eertwegh et al and Roy et al. to those of Schrader et al., Burkly et al. and Wilson et al. as well as to those of Black et al. to screen and obtain antagonistic anti-gp39 antibodies with the ability to inhibit cytokines produced by activated T cells, including the inhibition of IL-2, IL-4 and γ-interferon, which were known to be products of the T cells targeted by antagonistic anti-gp39 antibodies. According to Black et al., a person of ordinary skill in the art would have been motivated to produce this resultant ability of anti-gp39 antibodies to inhibit cytokine activity by activated T cells in order to test and select for those anti-gp39 antibodies that had the described properties of inhibiting gp39:CD40 interaction and the resultant ability of such antibodies to inhibit T cell mediated activation of immune response in the treatment of various conditions and disorders, including multiple sclerosis. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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